

**REMARKS**

This is a full and timely response to the Office Action mailed August 24, 2004

By this Amendment, claims 1-3 have been amended to put the claims in better form and to more particularly define the present invention. Further, claims 4-6 and 10-12 have been canceled without prejudice or disclaimer to its underlying subject matter. Support for claim amendments can be found throughout the specification and the original claims. Thus, claims 1-3 and 7-9 are currently pending for the Examiner's consideration, with claims 7-9 being withdrawn.

Applicant believes that all pending claims are in condition for allowance. Reexamination and reconsideration in light of the above amendments and the following remarks is respectfully requested.

**Restriction Requirement**

In response to the restriction requirement set forth in the Office Action, Applicant hereby affirm the election of Group I, claims 1-6 and 10-12, for examination. Applicant, of course, also reserves the right to file a divisional application covering the subject matter of the non-elected claims.

**Rejections under 35 U.S.C. § 112**

Claims 1-6 are rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Applicant respectfully traverses this rejection.

However, in order to expedite prosecution, Applicant has amended claims 1-3 and canceled claims 4-6 to address the Examiner concerns. In particular, the term “*artificial cartilage*” has been deleted from the pending claims. Further, the phrase “*cartilage differentiation inducing medium*” has been amended to “*differentiation inducing medium*” which resolves the Examiner confusion.

Thus, in view of the amendments to the claims, withdrawal of this rejection is respectfully requested.

Claims 10-12 are rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness which has been rendered moot by the cancellation of claims 10-12.

**Rejection under 35 U.S.C. § 102**

Claims 4-6 are rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Kandel (U.S. Patent 5,326,357), Parvizi et al., Nishikori et al. and Pittenger et al. (WO 98/32333). This rejection has been rendered moot by the cancellation of claims 4-6.

**Rejections under 35 U.S.C. § 103**

Claims 1, 2, 10 and 11 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Pittenger et al. (WO 98/32333) in view of Parvizi et al. Applicant respectfully traverses this rejection with regard to claims 1 and 2. For claims 10 and 11, this rejection has been rendered moot in view of the cancellation of claims 10 and 11.

To establish a *prima facie* case of obviousness, the prior art references must either alone or in combination teach the invention as a whole, including all the limitations of the claims. Here, in this case, the cited reference, in combination, fails to teach or suggest the limitation “**irradiating said undifferentiated mesenchymal cells with ultrasound to accelerate the differentiation of said undifferentiated mesenchymal cells to chondrocyte cells**” (emphasis added).

Pittenger et al. teaches manufacturing artificial cartilage, comprising culturing undifferentiated mesenchymal stem cells in a chondroinductive medium that contains TGF-β3. Parvizi et al. teach irradiating **a culture of chondrocyte cells** with ultrasound to increase aggrecan m-RNA and protein by chondrocytes. However, both Pittenger et al. and Parvizi et al. fail to teach or suggest irradiating **undifferentiated mesenchymal cells** with ultrasound.

Further, a *prima facie* case of obviousness also requires some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. A prior art reference that “teaches away” from the claimed invention is a significant factor to be considered in determining obviousness. In other words, it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

Here, in this case, Parvizi et al. teach away from irradiating undifferentiated mesenchymal stem cells with ultrasound since Parvizi et al. teach only irradiating a culture of chondrocyte cells. Thus, one skilled in the art, based on the teachings of Parvizi et al., would not be motivated to irradiate undifferentiated mesenchymal stem cells with ultrasound since such teaching is not found in any of the cited references.

It should also be noted that a *prima facie* case of obviousness based on similarity of methods is rebuttable by proof that the claimed method possess unexpectedly advantageous or superior properties. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). In the Examples of the present specification, the Applicants have shown that amount of aggrecan in the mesenchymal stem cells of Group 3 (TGF- $\beta$  3(+)/ultrasound (+)) are increased about 1.85 times as high as Group 2 ( TGF- $\beta$  3(+)) by the treatment of ultrasound for ten days. Histological examination (Fig. 4) shows that pellets treated with both TGF  $\beta$  3 and ultrasound (Group 3) is strongly stained with alcian blue as well as pellets treated with only TGF- $\beta$  3 (Group 2). Especially the bottom half of Group 3 are better stained than TGF- $\beta$ -treated pellets (Group 2). Immunostaining pattern for aggrecan (Fig. 5) shows a similar result to those of alcian blue. These results indicate that TGF- $\beta$  induces chondrocyte differentiation of mesenchymal stem cells in the pellets, and that ultrasound treatment accelerates the differentiation treatment. Such a result is unexpected and superior to that which is taught in the cited references.

Thus, for these reasons, this rejection cannot be sustained and should be withdrawn.

Claims 1-3 and 10-12 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Pittenger et al. (WO 98/32333) in view of Nishikori et al. Applicant respectfully traverses this rejection with regard to claims 1-3. For claims 10-12, this rejection has been rendered moot in view of the cancellation of claims 10-12.

As stated above, Pittenger et al. teaches manufacturing artificial cartilage, comprising culturing undifferentiated mesenchymal stem cells in a chondroinductive medium that contains TGF-  $\beta$ 3. However, it fails to teach or suggest irradiating undifferentiated mesenchymal cells with ultrasound. Like Parvizi et al., such a deficiency is not cured by the teachings of Nishikori et al. since it also teaches irradiating *cultures of chondrocyte cells* with ultrasound. Nishikori et al.

irradiates *cultures of chondrocyte cells* with ultrasound to increase chondroitin sulfate synthesis by the chondrocytes. Thus, the combination of Pittenger et al. (WO 98/32333) and Nishikori et al. cannot render obvious the present claims since they, in combination, fail to teach or suggest all the limitations of the claims.

Further, for the same reasons as discussed above, one skilled in the art, based on the teachings and suggestions of Nishikori et al., would not be motivated to irradiate undifferentiated mesenchymal stem cells with ultrasound since such teaching or suggestion is not found in both Pittenger et al. and Nishikori et al.

Lastly, to further demonstrated the unexpected superior results of the present invention, Nishikori et al. teaches that the chondroitin sulfate content in ultrasound-treated group are twice as high as those in the control group, after 3 weeks of culture of chondrocytes (see Table I of Nishikori et al.). The experimental data of the present specification shows that ultrasound treatment accelerates the chondrocyte differentiation of mesenchymal stem cells during the culture of 10 days.

Thus, withdrawal of the present rejection is respectfully requested.

Claims 10 and 11 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Pittenger et al. (WO 98/32333) in view of Wu et al. This rejection has been rendered moot by the cancellation of claims 10 and 11.

### CONCLUSION

For the foregoing reasons, all the claims now pending in the present application are believed to be clearly patentable over the outstanding rejections. Accordingly, favorable reconsideration of the claims in light of the above remarks is courteously solicited. If the Examiner has any comments or suggestions that could place this application in even better form, the Examiner is requested to telephone the undersigned attorney at the below-listed number.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-0013, under Order No. TEI-0128 from which the undersigned is authorized to draw.

Dated: November 24, 2004

Respectfully submitted,

By 

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 180013 for any such fees; and applicant(s) hereby petition for any needed extension of time.